REMARKS

Claims 1-14, 22, and 23 are pending in the application. Claims 14, 22, and 23 were withdrawn from consideration, leaving claims 1-13 subject to examination. Claims 1-3 and 6-13 were rejected under 35 U.S.C. § 112, first paragraph; claims 1-3, 6, and 8-13 were rejected under 35 U.S.C. § 102(e); and claims 1, 3-7, 10, and 11 were rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed as follows.

Restriction Requirement

The Restriction Requirement has been made final. In particular, the Examiner maintains that the technical feature linking the inventions of Groups I and II does not constitute a special technical feature, as defined by PCT Rule 13.2, as it does not define a contribution over US 2002/0071832. Applicants respectfully disagree because, as is discussed below in connection with the rejection under 35 U.S.C. § 102(e) over the cited reference, the present invention is novel over this reference, thus defining a contribution over the prior art. Applicants thus request reconsideration of the Restriction Requirement. Applicants further note that each of the claims of both Groups I (claims 1-13) and II (claims 14, 22, and 23) are readable on the elected species.

Specification

The specification was objected to on the basis that the abstract of the disclosure does not commence on a separate sheet. This objection has been met by the present amendment to the specification, which adds the abstract present in the corresponding PCT publication (WO 03/073918) to a new page.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-3 and 6-13 were rejected under § 112, first paragraph as failing to comply with the written description requirement. The Examiner states that the specification does not support the previously submitted amendment to claim 1, in which the term "metastasis" was inserted into the following phrase "method of preventing or treating metastasis of cancer in a subject." Applicants respectfully disagree with this rejection because, as is discussed below, the concept of preventing and treating metastasis of cancer in a subject is described in the application.

For example, at page 2, lines 9-12 the specification describes the prevention or treatment of cancer metastasis as follows:

> "The administered herpes virus prevents or treats the recurrence of any cancer that may remain at the site of resection, as well as prevents or treats any cancer that may have metastasized from the site of surgical resection." (Emphasis Added).

Further, at page 2, lines 25 and 26, the specification states:

> "Thus, the methods of the invention can be used to treat primary tumors, as well as to prevent lymphatic metastases." (Emphasis Added).

At page 4, line 33 through page 5, line 3, the specification states:

> "The administered herpes virus also enters the lymphatic system from the site of primary tumor in the same manner as any potentially metastasizing tumor cells, thus enabling the treatment and prevention of metastasis from the primary tumor site." (Emphasis Added).

As another example, at page 10, lines 1-4, the specification states:

> "This study investigates the use of an attenuated, replication-competent, oncolytic herpes virus (NV1023), both to treat a primary tumor by direct injection, and to travel through the lymphatic system to treat metastatic tumors within the lymph nodes draining lymph from the site of primary cancer." (Emphasis Added).

Thus, as it is clear that the prevention and treatment of metastasis of cancer is described in the specification, Applicants request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 102(e)

Claims 1, 2, 6, and 8-13 were rejected under § 102(e) as being anticipated by Fong et al., US 2002/0071832, on the basis that this reference teaches a method of resecting a tumor from a patient and injecting a virus into the tumor bed to ensure destruction of any remaining tumor cells. Applicants respectfully disagree with this rejection, as the cited reference does not describe what is claimed. In particular, the Fong reference does not describe the prevention and treatment of cancer metastasis at a site distal to the site of surgical resection of a tumor, by herpes simplex virus administration to the resection site.

As is well-established in the art, "metastasis" is the spread of cancer from a primary site to one or more other sites within the body (see, e.g., definitions provided in accompanying excerpts provided from The British Columbia Cancer Agency and Wikipedia). In contrast to the teachings of the cited reference, in which herpes viruses are suggested for use in destroying tumor cells at the site of resection, according to the present invention, the administered herpes viruses travel from the site of resection, destroying any cancer cells that may have metastasized from the tumor. Thus, the cells targeted according to the methods of the present invention and the cited reference have different spatial localizations: the site of resection (cited reference) and a locus distal to the site of resection (present invention).

And it is not only with respect to the locations of the target tumor cells that the methods of the present invention differ from that mentioned in the cited reference. Indeed, the very

natures of the targeted cells differ as well. In particular, tumors having metastatic potential generally are highly heterogeneous, and it is only certain cells within such tumors that have the capability to successfully form metastases, due to their unique abilities to overcome substantial obstacles to metastasis (see, e.g., Fiddler et al., Hospital Practice, July 1982, p. 57-64; a copy is enclosed). For example, such cells must detach from a primary tumor, gain entrance into circulation, survive in circulation, arrest at an organ capillary bed, extravasate, and grow in a new site, all the while evading host inflammatory and immune system mediators (Fiddler et al., supra). Most cells within a tumor do not undergo such actions.

Further, it has been reported that tumor cells that form viable metastases may represent 1% or less of tumor cells that leave the site of a primary tumor (Schirrmacher, Advances in Cancer Research 43:1-64, 1985; a copy is enclosed). Thus, only a fraction of the cells of a primary tumor leave the tumor, and only a very small portion of these leaving cells form viable metastases. It thus follows that most cells within a tumor do not and likely cannot form metastases. It is these latter cells that are the target of the method mentioned in the cited reference: cells that may, if left in the tumor bed, continue to grow and form another tumor at the site of resection. The other, more specialized and rare cells, which may form metastases (and which are the subject of the present claims), are not mentioned in the cited reference.

Thus, as the claimed methods are different from that mentioned in the cited reference, the present rejection should be withdrawn.

Claims 1-3, 6, 8, 9, 12, and 13 were rejected under § 102(e) as being anticipated by Molnar-Kimber et al., U.S. Patent No. 6,428,968. The Examiner states that this reference teaches killing tumor cells of a subject by administration of a herpes virus and a chemotherapeutic agent

and, referring to column 2, "the method can be used following surgical excision or for inhibiting growth of immature metastases by killing tumor cells distributed throughout the body." Applicants respectfully disagree with this characterization of the reference, and submit that it does not anticipate the present claims, as follows.

Molnar-Kimber does not teach the prevention or treatment of cancer metastasis at a distal site by administration of herpes viruses to a site of surgical resection, as is now claimed. Rather, in the passage cited by the Examiner in this rejection (column 2), Molnar-Kimber describes a study in which a particular herpes simplex virus, HSV-1716, was administered to an animal model of malignant mesothelioma by intraperitoneal injection. In characterizing the study, Molnar-Kimber states "... tumor cells were not completely eradicated from the test subjects. Thus, the subjects were not cured of cancer, even though their tumor burden was significantly reduced."

Molnar-Kimber concludes by stating that "these therapies remain amenable to improvement, and that supplemental treatments may remain necessary to prevent re-establishment of nearly ablated tumors, to kill residual tumor cells following surgical tumor excision, and to inhibit growth of immature metastases by killing tumor cells distributed throughout the body of a subject." Molnar-Kimber does not state what such "supplemental treatments" may be, but it is clear that, by stating that treatments in addition to the described herpes simplex virus treatment may be necessary, Molnar-Kimber is not describing the use of herpes simplex viruses for this purpose. Even if such treatments were specified to be further herpes virus treatments (which they are not), there is no mention of administration to the site of surgical resection, as in the present claims. Further, this discussion of Molnar-Kimber is in the

section of the patent describing the problems of the state of art, and is not proposing any solutions to such problems. Thus, the Molnar-Kimber patent does not describe the presently claimed invention, and the present rejection should therefore be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 6, and 7 were rejected for obviousness over Fong et al., US 2002/0071832, in combination with Wong et al., Human Gene Therapy 12(3):253-265, 2001. This rejection is respectfully traversed.

The Fong patent application publication is cited for teaching the application of herpes simplex virus to the site of resection of a tumor, as noted above. The Examiner states "destruction of any remaining tumor cells would read on the preamble of the claim because destruction of remaining tumor cells would prevent tumor cells from metastasizing from the tumor bed." The Wong reference is cited for teaching herpes simplex virus NV1023. The Examiner concludes that it would have been obvious to use NV1023, as taught by Wong, in the method of Fong, because Wong teaches that NV1023 is an attenuated, replication-competent, oncolytic herpes simplex virus. Applicants respectfully disagree with this rejection.

As is discussed above, Fong does not teach the treatment or prevention of cancer metastasis. Rather, Fong mentions destruction of tumor cells at the site of resection, to prevent re-growth of tumor cells and reformation of a tumor at the site of resection. This is very different from the presently claimed invention, in which the focus is not the activity of administered virus at the site of resection, but at distal sites to which certain tumor cells may have migrated and not tumor cells as they remain at the surgical site. As is discussed in detail above, tumors including

cells that have the potential to metastasize are highly heterogeneous, and from such tumors it has been reported that only 1% or less of even the cells that leave the primary tumor site survive to become viable metastases (Fidler, supra; Schirrmacher, supra). Thus, Fong's mention of virus administration to a surgical bed does not provide any suggestion or motivation to treat metastases, which is the focus of the present claims. Indeed, prior to the present invention, the surprising activity of herpes simplex viruses in treating metastases was not known or predictable. Thus, it would not have been obvious to use any herpes simplex virus, not to mention NV1023, in a method for preventing or treating metastasis at a distal site. Applicants thus request that this rejection be withdrawn.

Claims 1, 6, 7, 10, and 11 were rejected under § 103(a) for obviousness over Molnar-Kimber et al., U.S. Patent No. 6,428,968, in combination with Wong et al., Human Gene Therapy 12(3):253-265, 2001. This rejection is respectfully traversed.

The Examiner states that the Molnar-Kimber patent teaches killing tumor cells by administration of herpes simplex viruses and chemotherapeutic agents, and that such a method can be used following surgical excision or for inhibiting growth of immature metastases by killing tumor cells distributed throughout the body, as is noted above. The Wong reference is cited for teaching herpes simplex virus NV1023. The Examiner concludes that it would have been obvious to use NV1023, as taught by Wong, in the method of Molnar-Kimber, because Wong teaches that NV1023 is an attenuated, replication-competent, oncolytic herpes simplex virus. Applicants respectfully disagree with this rejection.

As is discussed above in reference to the rejection under § 102(e) over Molnar-Kimber, the cited patent does not describe the administration of herpes simplex viruses to the of site

surgical resection to prevent or treat cancer metastasis. Rather, as is discussed above, the passage cited by the Examiner on this point (column 2) describes a study of intraperitoneally administered herpes virus, and notes that because residual tumor cells remain after such treatment, some type of unspecified, "supplemental" treatments may be required for effective treatment. Thus, similar to the Fong reference, discussed above, Molnar-Kimber does not suggest or provide motivation for the administration of a herpes virus to the site of surgical resection, not to mention NV1023. This rejection should therefore be withdrawn.

Claims 1, 3, and 5 were rejected for obviousness over Cole et al., U.S. Patent No. 5,162,231, in combination with Molnar-Kimber et al., U.S. Patent No. 6,428,968, and Johnston et al., Ann. Thorac. Surg. 71:1120-1125, 2001.

The Cole patent is cited for teaching the recurrence of malignant lesions or metastasis in lung cancer, even after surgical resection. The Examiner cites the Molnar-Kimber patent in this rejection, stating that it teaches herpes simplex virus administration following surgical excision, and thus use of this method for enhancing the treatment of lung cancer. The Johnston reference is cited for teaching that lung tumors spread to lymph nodes. The Examiner states that it would have been obvious to combine the teachings of these references to enhance the treatment of resected lung cancer in a patient. Applicants respectfully disagree.

As is noted above, the Molnar-Kimber patent does not teach administration of herpes simplex viruses to the site of surgical excision. Rather, the method of Molnar-Kimber involves intratumoral injection. The only mention in Molnar-Kimber of residual cancer cells present in a site of tumor resection is in noting that some type of unspecified, "supplementary" treatment may be required to address such cells in the context of administration of a herpes simplex virus

administered by intraperitoneal injection to treat malignant mesothelioma. Neither of the other cited references suggests or provides motivation for administration of a herpes simplex virus to the site of tumor resection. Applicants thus submit that this rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Although no charges are believed to be due, if there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Susan M. Michaud

Susan M. Michaud, Ph.D.
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045